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(54) Title: USE OF GABA ANTAGONISTS IN THE TREATMENT OF EMESIS

(57) Abstract

The present invention relates to the use of selected GABA agonists having an agonist action at $GABA_B$ receptors in the treatment of emesis.

Exhibit C

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Novel Medical Use for GABA Agonists

The present invention relates to the use of γ-aminobutyric acid (GABA) agonists having an agonist action at $GABA_B$ receptors in the treatment of emesis.

GABA is an endogenous inhibitory neurotransmitter in the CNS and peripheral nervous systems. Receptors for GABA have been divided into $GABA_A$ and $GABA_B$ receptor sub-types. $GABA_B$ agonists are described as being of use in the treatment of CNS disorders, such as muscle relaxation in spinal spasticity, cardiovascular disorders, asthma, gut motility disorders such as irritable bowel syndrome and as prokinetic and anti-tussive agents.

It has now been found that GABA agonists having an agonist action at $GABA_B$ receptors are useful in the treatment of emesis. Our co-pending PCT Patent Application No. PCT/EP94/01319 relates to the use of GABA agonists having an agonist action at $GABA_B$ receptors in the treatment of emesis.

The use of the GABA agonists having an agonist action at $GABA_B$ receptors specifically disclosed in co-pending PCT Patent Application No. PCT/EP94/01319 in the treatment of emesis is not included within the scope of the present invention.

The invention accordingly provides, in a first aspect, the novel use of a GABA agonist having an agonist action at $GABA_B$ receptors, selected from the compounds β-phenyl-γ-aminobutyric acid (β-phenyl-GABA), 3-amino-2-(4-chorophenyl)-nitropropane, 1-(aminomethyl)cyclohexaneacetic acid (gabapentin) and 3-aminopropyl phosphonic acid, or a compound generically or specifically disclosed in published European Patent Application No. EP82369, PCT Patent Application Nos. WO93/11138, WO93/22314 or US Patent Specification Nos. US3896149, US4952573, US5182290, US5281747 (excluding the compound (3-aminopropyl)methylphosphinic acid) or British Patent Specification No. 2185483, such as D-N-(2-pyrrolidone-5-carbonyl)-piperidine, in the treatment of emesis.

There is also provided as a further aspect of the invention the use of the GABA agonists having an agonist action at $GABA_B$ receptors listed above and generically and specifically disclosed in the above referenced patent specifications in the preparation of a medicament for use in the treatment of emesis.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, suffering from or susceptible to emesis, comprising administration of an effective amount of a GABA agonist having an agonist action at $GABA_B$ receptors listed above or generically or specifically disclosed in the above referenced patent specifications.

It will be appreciated by those skilled in the art that certain of the compounds listed above and generically or specifically disclosed in the above referenced patent specifications contain chiral centres and thus exist in the form of pairs of enantiomers. All isomers of these compounds and mixtures thereof, including racemic mixtures, are included as compounds for use in the instant invention.

There is an isolated report (The Lancet, July 23, 1983, pg. 227) that baclofen reduced the frequency of vomiting due to duodenal ileus in a patient with Duchenne muscular dystrophy. For the avoidance of doubt, it is submitted that the use of (±) baclofen in the treatment of emesis caused by duodenal ileus is not included within the scope of the instant invention.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

GABA agonists having an agonist action at $GABA_B$ receptors have been shown to have anti-emetic activity as indicated by for example their ability to inhibit emesis induced by a variety of emetogens in the ferret.

The treatment of emesis mentioned hereinbefore includes the treatment of nausea, retching and vomiting. Emesis includes acute emesis, delayed or late emesis and anticipatory emesis. GABA agonists having an agonist action at $GABA_B$ receptors are useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic

agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5-fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intercranial pressure; decreased intercranial pressure (e.g. altitude sickness); and opioid analgesics, such as morphine; and gastro-oesophageal reflux disease, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn and dyspepsia.

$GABA_B$ agonists may be administered as the raw chemical but are preferably presented as a pharmaceutical formulation. Suitable pharmaceutical formulations for $GABA_B$ agonists are described in the art, for example as in the above referenced patent specifications.

For example $GABA_B$ agonists may be formulated for oral, buccal, parenteral, depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose). Oral and parenteral formulations are preferred.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known

in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The $GABA_B$ agonists may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The $GABA_B$ agonists may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The $GABA_B$ agonists may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an

acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the $GABA_B$ agonists may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

Suitable dose ranges are described in the art, that is to say that for use as anti-emetics the compounds may be used at doses appropriate for other conditions for which $GABA_B$ agonists are known to be useful. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient, and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected. A suitable dose range is for example 0.1 mg/kg to about 200 mg/kg, e.g. 0.1 mg/kg to 10 mg/kg, bodyweight per day.

The $GABA_B$ agonists having an agonist action at $GABA_B$ receptors useful in the instant invention may, if desired, be administered in combination with one or more other therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art. For example, GABA agonists having an agonist action at $GABA_B$ receptors may be administered in combination with a systemic anti-inflammatory corticosteroid such as methyl prednisolone or dexamethasone, a $5HT_3$ antagonist such as ondansetron, granisetron or metoclopramide, or a tachykinin antagonist, including substance P antagonists and other neurokinin antagonists, such as an NK_1 receptor antagonist, or a sympathomimetic such as ephedrine, pseudoephedrine or oxymetazoline.

Reference Example

The anti-emetic activity of the $GABA_B$ agonist (±) baclofen was demonstrated by its ability to inhibit emesis induced by radiation, cisplatin, morphine and ipecacuanha in the ferret.

The anti-emetic activity of R(-) baclofen (active isomer) was demonstrated by its ability to inhibit radiation-induced emesis in the ferret.

Radiation Test

In this model of emesis the onset of retching and vomiting occurs approximately 20 minutes after whole body irradiation (2 Grey ≡ 200 Rads). The test compound is administered (e.g. i.p., p.o., i.v., s.c.) immediately after irradiation and its effect on emesis determined by comparison with appropriate controls.

(±) Baclofen inhibited emesis in the above test at 3mg/kg p.o. and 1mg/kg s.c. R(-) Baclofen inhibited emesis in the above test at 0.5 mg/kg s.c. S(+) Baclofen (inactive at $GABA_B$ receptors) failed to inhibit emesis at 0.5 mg/kg s.c.

Cisplatin Test

In this model of emesis the onset of retching and vomiting occurs approximately 1 hour after the administration of cisplatin (200mg/m^2 i.p.). The test compound was administered (s.c.) 1 hour after the administration of the emetogen and its effect on emesis determined by comparison with appropriate controls (e.g. water).

(±) Baclofen inhibited emesis in the above test at 1.0 mg/kg s.c.

(±) Baclofen inhibited ipecacuanha - and morphine-induced emesis in ferrets at 1.0 mg/kg s.c.

Claims

1. The use of a GABA agonist having an agonist action at $GABA_B$ receptors, selected from the compounds β-phenyl-γ-aminobutyric acid, 3-amino-2-(4-chorophenyl)-nitropropane, 1-(aminomethyl)cyclohexaneacetic acid and 3-aminopropyl phosphonic acid, or a compound generically or specifically disclosed in EP82369, WO93/11138, WO93/22314, US3896149, US4952573, US5182290, GB2185483, or US5281747, excluding the compound (3-aminopropyl)methylphosphinic acid, in the preparation of a medicament for use in the treatment of emesis.

2. The use according to claim 1 wherein the GABA agonist is selected from β-phenyl-γ-aminobutyric acid, 3-amino-2-(4-chorophenyl)-nitropropane, 1-(aminomethyl)cyclohexaneacetic acid, 3-aminopropyl phosphonic acid and D-N-(2-pyrrolidone-5-carbonyl)-piperidine.

3. The use according to Claim 1 or Claim 2 wherein said emesis is induced by cancer chemotherapeutic agents, radiation sickness, radiation therapy, poisons, toxins, pregnancy, vestibular disorders, post-operative sickness, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain, migraine, increased intercranial pressure, decreased intercranial pressure, or opioid analgesics.

4. The use according to Claim 3 wherein said emesis is induced by a cancer chemotherapeutic agent, radiation sickness or radiation therapy.

5. The use according to Claim 4 wherein said cancer chemotherapeutic agent is selected from cyclophosphamide, carmustine, lomustine, chloroambucil, dactinomycin, doxorubicin, mitomycin-C, bleomycin, cytarabine, methotrexate, 5-fluorouracil, etoposide, vinblastine, vincristine, cisplatin, decarbazine, procarbazine, hydroxyurea, and combinations thereof.

6. The use according to Claim 5 wherein said emesis is induced by cisplatin.

7. The use according to Claim 5 wherein said emesis is induced by cyclophosphamide.

8. The use according to Claim 1 or Claim 2 wherein said emesis is induced by morphine or ipecacuanha.

9. A method for the treatment of a mammal, including man, suffering from or susceptible to emesis, comprising administration of an effective amount of a GABA agonist having an agonist action at $GABA_B$ receptors, selected from the compounds β-phenyl-γ-aminobutyric acid, 3-amino-2-(4-chorophenyl)-nitropropane, 1-(aminomethyl)cyclohexaneacetic acid and 3-aminopropyl phosphonic acid, or a compound generically or specifically disclosed in EP82369, WO93/11138, WO93/22314, US3896149, US4952573, US5182290, GB2185483, or US5281747, excluding the compound (3-aminopropyl)methylphosphinic acid.